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The first total synthesis of mauritine-A

Taoues Laïb, Michèle Bois-Choussy and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

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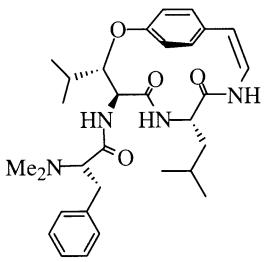
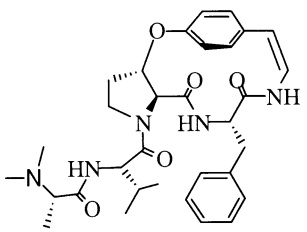
Abstract

Total synthesis of mauritine-A is accomplished featuring a key cycloetherification reaction based on an intramolecular S_NAr reaction.

Cyclopeptide alkaloid is a family of 13-, 14- and 15-membered cyclophanes widely distributed among plants of the Rhamnaceae.[1] Since the first structural determination of pandamine by Goutarel and Païs in 1966,[2] this family of natural product has grown rapidly and encompasses nowadays a group of over 200 compounds. Although various bioactivities have been identified,[1] their limited availability from natural sources has hampered extensive pharmacological investigations and, consequently, their biological profile has not yet been well defined. Nevertheless, sanjoinine-A (frangufoline) (**1**) has been identified as the major bioactive component, responsible for the sedative properties of 'Sanjoin', a plant seed of clinical importance in oriental medicine.[3]



1 Sanjoinine A



2 mauritine-A

Synthesis of cyclopeptide alkaloids has been investigated by a number of groups and various ingenious approaches have been investigated.[4] A seminal contribution results from Schmidt's group who discovered that activation of a carboxyl group via a pentafluorophenyl ester is particularly effective for the ring closure reaction. Based on this methodology, the same group has accomplished the first total synthesis of zizyphine-A,[5] mucronin-B[6] and finally frangulanine,

* Corresponding author. Fax: 33 1 69 07 72 47; e-mail: zhu@icsn.cnrs-gif.fr

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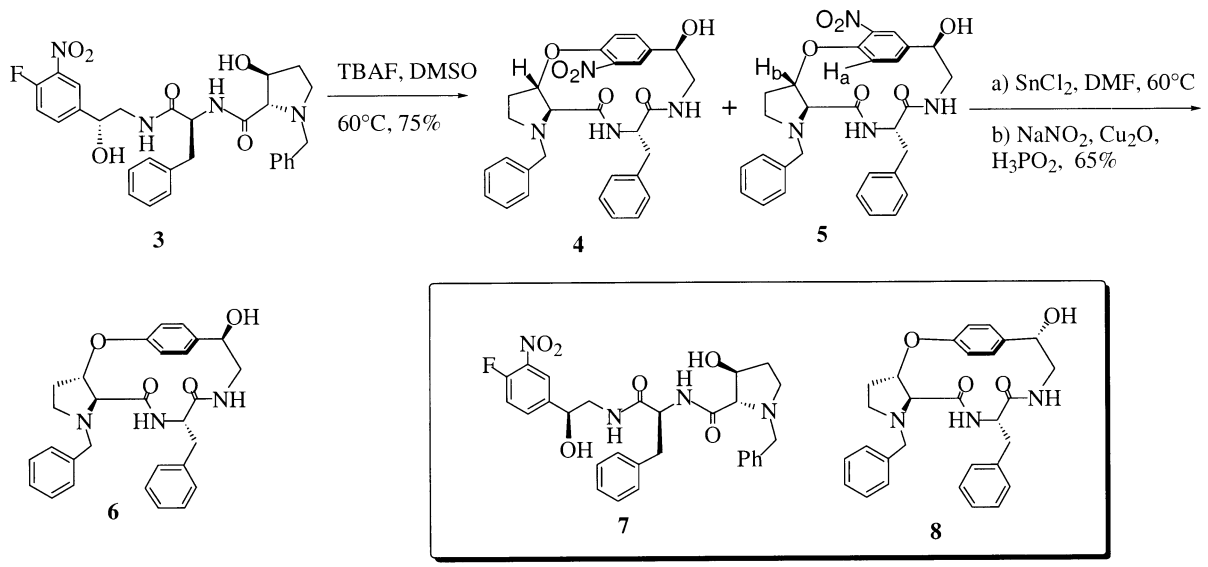
a 14-membered *para*-cyclophane in 1991.[7] Subsequently, other natural products have been synthesized in Joullié's[8] and Han's[9] groups employing the same macrolactamization strategy.

Despite these impressive achievements, there is still a need for developing a more practical and efficient synthetic route to this class of natural products. Toward this end, we have developed a novel cycloetherification methodology[10] and have recently achieved an asymmetric total synthesis of sanjoinine G1.[11] In this letter, we describe the first total synthesis of mauritine-A (**2**),[12] isolated by Tschesche from the root bark of *Ziziphus mauritiana* Lam.[13] Formation of an aryl–alkyl ether bond with concomitant ring closure based on an intramolecular S_NAr reaction[14] is the key feature of the present synthesis.

The cyclization precursor **3** was prepared by two conventional peptide coupling steps starting from (1*R*)-1-(4′-fluoro-3′-nitro)phenyl-2-aminoethanol,[15] L-*N*-Boc phenyl ala and (2*S*,3*S*)-*N*-benzyl-2-hydroxy proline.[16] Cyclization of dipeptide **3** under the optimal conditions (TBAF, DMSO, 60°C) afforded 14-membered cyclophane in 75% yield as a mixture of two atropisomers **4** and **5** in a 1/1.5 ratio. A strong NOE correlation observed between protons H_a and H_b is indicative of the atropstereochemistry of compound **5**. Steric repulsion between a nitro group and an *N*-benzyl residue of proline in compound **4** may be responsible for the preferential formation of the atropisomer **5**. The fact that compounds **4** and **5** are two atropisomers was confirmed by their subsequent transformation to the common product **6** via a straightforward two-step sequence (Scheme 1).

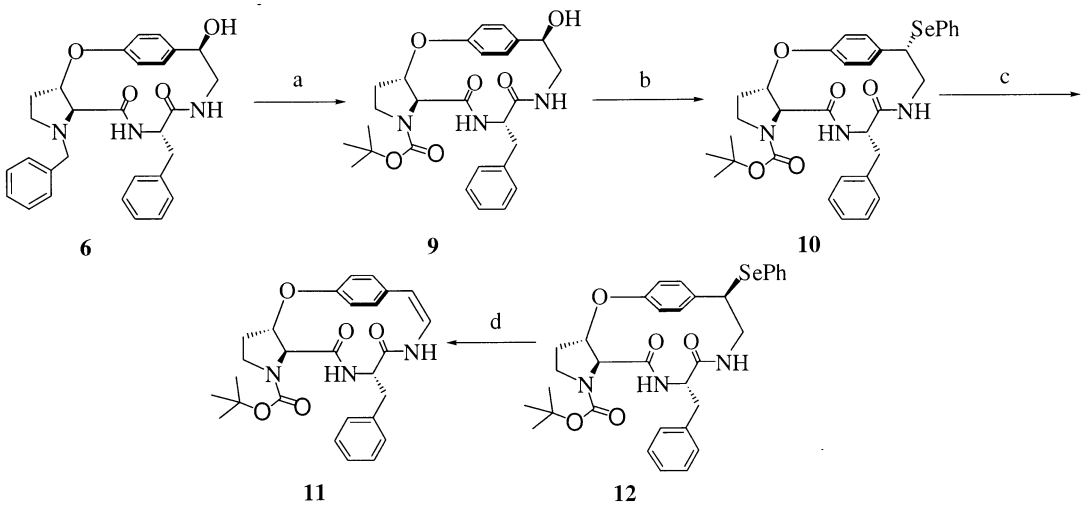


Scheme 1.

To verify if the stereochemistry of benzylic alcohol can exert any influence on the macrocyclization reaction and the subsequent dehydration reaction at the benzylic carbon, compound **7**, an epimer of **3**, was synthesized and was transformed into cyclophane **8** following the identical synthetic scheme. The same efficiency observed indicated that neither the cyclization nor the post-manipulations of nitro groups were sensitive to the stereochemistry of the tether chain.

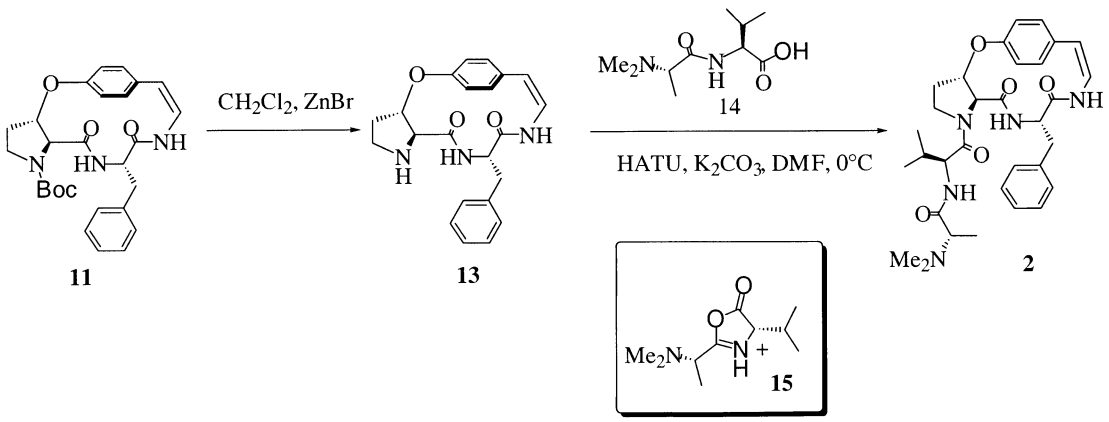
Prior to the introduction of the enamide function, the *N*-protective group of proline residue needed to be readjusted. This was realized by a one-step transprotection procedure. Thus, hydrogenolysis of compound **6** over Pearlmans catalyst in the presence of Boc_2O gave the

corresponding *N*-Boc derivative (**9**).[17] The benzylic hydroxyl function was stable under these conditions (Scheme 2). Mesylation of alcohol followed by its displacement with sodium phenyl selenide gave compound **10**. This substitution reaction was hypothesized to proceed via an S_N2 mechanism. In fact, as seen from the X-ray structure of mauritine-A,[18] the benzylic carbon was out of the plane defined by the aromatic ring due to the presence of severe ring strain. Consequently, stabilization of the possible carbon cation intermediate by the benzene ring was virtually non-existent rendering the S_N2 reaction more plausible. This particular structural property can also explain the stability of benzylic alcohol under the hydrogenation conditions. Oxidation of phenyl selenide with hydrogen peroxide in CH_2Cl_2 in the presence of pyridine gave the corresponding selenoxide, which was found to be unstable and underwent the desired *syn*-elimination to afford directly the enamide **11** at room temperature. In contrast, the phenylselenoxide resulting from the oxidation of *R* configured selenide **12** was more stable and heating in benzene was required to effect the desired *syn*-elimination.[7,8] Our results unambiguously established that the *R* configured secondary alcohol **9** is much easier to undergo *syn*-elimination via phenylselenoxide than the *S* configured alcohol **8**.



Scheme 2. *Reagents and conditions*: (a) $Pd(OH)_2$, H_2, Boc_2O, ^tBuOH, 90%; (b) (i) MsCl, Et_3N, CH_2Cl_2, −10°C, (ii) diphenyl diselenide, $NaBH_4$, 5°C, then 80°C, 72%; (c) H_2O_2, Py., CH_2Cl_2, 25°C, 60%; (d) H_2O_2, Py., CH_2Cl_2, then benzene, 60°C, 55%

To reach the mauritine-A, a two-step sequence involving *N*-deprotection and peptide coupling was required. These seemingly trivial transformations were found to be more difficult than it might suggest. Joullié[8c] has previously identified Ohfune's procedure (TMSOTf, 2,6-dimethyl lutidine) for the removal of the *N*-Boc function.[19] However, only degradation was observed when these conditions were applied to compound **11**. After surveying various conditions, the procedure developed by Mann ($ZnBr_2$, CH_2Cl_2)[20] was found to be the most suitable in this case. Coupling of **13** with dipeptide *N*,*N*-dimethyl-L-alanyl-L-valine (**14**)[12] posed another problem due to the racemization at the valine α-carbon, probably via the münchnone intermediate **15**. Model coupling between L-proline methyl ester and dipepetide **14** revealed that HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) in DMF in the presence of K_2CO_3 was optimal.[8,21] Applying these two optimized deprotection–coupling conditions to compound **10**, mauritine-A was obtained in 20–40% yield (Scheme 3).



Scheme 3.

In conclusion, we achieved the first total synthesis of mauritine-A using cycloetherification technology. Two difficult synthetic steps, namely, aryl–alkyl ether bond formation and macrocyclization associated with the synthesis of 14-membered cyclopeptide alkaloids were reduced into a single operation with high efficiency. Since the cyclization was performed on an intact peptidic precursor, the synthesis became very convergent. Furthermore, no tedious separation of diastereomers was required in contrast to previous syntheses.

Acknowledgements

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